

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kathleen C.M. Campbell

Art Unit: 1618

Serial No.: 10/694,436

Filed: October 27, 2003

Confirmation No.: 8942

For: THERAPEUTIC USE OF METHIONINE FOR THE
TREATMENT OR PREVENTION OF MUCOSITIS

Examiner: Shirley V. Gembeh

DECLARATION UNDER 37 C.F.R. § 1.132

I, James P. Malone declare as follows:

1. I am an Associate Professor and Residency Program Director in the Division of Otolaryngology at Southern Illinois University School of Medicine. I am board certified in Otolaryngology and my subspecialty training and expertise are in Head and Neck Surgery and reconstructive surgery of the head and neck. I received his medical degree from The University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania. I completed my residency in otolaryngology at The Pennsylvania State University in Hershey, Pennsylvania and a fellowship in head and neck surgical oncology and microvascular surgery at The Ohio State University in Columbus, Ohio.

2. In my review of the literature and experience treating patients, I have found that many patients undergoing radiation therapy do not develop mucositis. For example, radiation treatment is usually targeted to a specific area of the body wherein the diseased tissue is located. Thus, different side effects arise depending on the location of the diseased tissue. For example, oral mucositis may develop in patients receiving radiation treatment wherein oral mucosal tissue is in the field of the radiation exposure. In particular, oral mucositis commonly develops in treatment of cancers in the oral cavity or nasopharyngeal area due to the proximity of the oral mucosa to the tissues targeted by radiation treatment.

3. In contrast, when the diseased tissue targeted for radiation treatment is not in proximity to mucosal tissue, mucositis will generally not arise from the radiation treatment. By

way of example, radiation treatment of a breast tumor or tissue proximate to a surgically removed breast tumor does not ordinarily result in oral mucositis unless the location of the tumors and, more particularly, the pattern of radiation for treating diseased breast tissue, falls in at least close proximity to oral mucosa. Of course, radiation may cause problems other than oral mucositis in the tissue targeted. Examples of side effects arising from damage to healthy tissue, other than oral mucosal tissue, that is in the field of radiation exposure are appetite loss from radiation damage to brain cells, gastrointestinal disorders from radiation damage to cells in the gastrointestinal tract and/or abdomen, and neurotoxicity from damage to nerve cells. However, radiation exposing only portions of the gastrointestinal tract remote from the oral mucosa would rarely result in oral mucositis.

4. While oral mucositis is sometimes broadly classified as a form of gastrointestinal toxicity, oral mucositis is an effect distinctly separate from the effects ordinarily contemplated by "gastrointestinal toxicity" such as nausea, diarrhea and abdominal pain, and generally results from different pathological mechanisms. For example, the mucosa is the most highly differentiated layer of the GI tract. The mucosa generally consists of the epithelium, the lamina propria (i.e., the supporting loose connective tissue), the submucosa (i.e., deeper connective tissue that supports the mucosa) and the muscularis mucosae (i.e., thin layer of smooth muscle between the mucosa and submucosa). Tissue specialization and surface shape are correlated with functional differentiation along the tract. For example, in the oral cavity, the epithelium is protective, the lamina propria is unspecialized, and the muscularis mucosae are not present. In contrast, in the stomach, the gastric mucosa is specialized for production of digestive acid and enzymes and the mucosal surface of the epithelium consists of mucus-secreting cells for protection against self-digestion. In the small intestine, the intestinal mucosa is specialized for absorption of nutrients and surface area is increased.

5. Since the oral mucosal tissues are very different from the mucosal tissue in other parts of the gastrointestinal tract due to the different functions they perform, I would expect that the mechanisms of repair for these tissues in response to damage by radiation therapy would be different as well. Further, since the mechanisms of repair to radiation damage are different, I

would not expect that an agent that treats or supports repair of one type of tissue would necessarily treat or support repair of another type of tissue.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

James L. Caline Jr.

4/5/2010

Date